REMARKS

Restriction

In item 3 on page 2 of the Office Action, the Examiner states that claims 43, 45-54 are drawn to an invention nonelected without traverse in Paper #6, and further states that a complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action. Applicants point out that claims 43 and 45-54 are withdrawn from consideration for the time-being due to the species restriction, but that upon allowance of a generic claim, Applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim (Page 7, paragraph 4 of the restriction requirement mailed 2/15/2002). Applicants will demonstrate herein the patentability of generic claim 42, and hereby request reconsideration of species claims 43 and 45-54 which depend on that claim.

Claims 67-68 drawn to a nonelected invention are canceled herein, because it is not clear from the record whether these claims have officially been cancelled.

Amendments

Due to the 102(e) rejection, claims 42 and 63 now recite "Vinorelbine" as supported on page 20, line 11, for instance. Hence the cancellation of claims 59-62 and 64 as moot. In addition, because of the 112, 2nd paragraph rejections, the offending word "effective" is removed from claims 42 and 63 and the wording of claims 55-56 and 65-66 has been modified; those amendments are not believed to narrow claim scope. In that the amendments do not introduce new matter, entry thereof is respectfully requested.

Section 112, 2nd paragraph

Claims 42, 44, 55-56 and 59-66 are rejected under 35 USC Section 112, 2nd paragraph as allegedly being indefinite.

The word "effective" in claims 42, 59, 61 and 63 is considered to be indefinite.

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Without acquiescing in the rejection and in order to expedite prosecution, the offending word "effective" has been removed from claims 42 and 63, thus obviating this basis of the rejection as to those claims. Claims 59 and 61 are cancelled without prejudice or disclaimer, so the rejection of these claims is rendered moot.

The recitation of "cross-block" in claims 55-56 and 66 is believed to render the claims vague and indefinite.

Without acquiescing in the rejection and in order to expedite prosecution, claims 55-56 and 65-66 have been amended to refer to an antibody which binds to an epitope bound by 4D5, 7C2 or 7F3. Support for this language can be found on 12, line 24 through to line 7 on page 13. Reconsideration and withdrawal of this basis of the rejection is respectfully requested.

Section 112, 1st paragraph

Claims 42, 44, 55-56 and 59-66 are rejected under 35 USC Section 112, first paragraph on the basis that the specification, while being enabling for a method of *in vitro* treatment of tumor cell lines that overexpress HER2 comprising administration of anti-ErbB2 antibodies 4D5, 7C2 and 7F3, does not reasonably provide enablement for a method of *in vivo* treatment of tumors or cancers overexpressing ErbB2 with any anti-ErbB2 antibody and chemotherapeutics, wherein the antibody is able to cross-block. The Examiner relies on Seaver, S. *Genetic Engineering News* 14(14): 10 and 21 (1994) as teaching that despite the promising results of many monoclonal antibodies *in vitro*, their transition to *in vivo* therapy has met with some problems. The Examiner urges that the working examples of the instant invention are drawn to methods of *in vitro* cell death or induction of apoptosis caused by 4D5, 7C2 or 7F3; that no where does the specification teach how to use any other antibody for the treatment of cancer or tumors in an *in vivo* capacity, and based on the teachings of unpredictability regarding *in vivo* therapy which are taught in the prior art, persons skilled in the art would not associate *in vitro* results with *in vivo* therapeutic efficacy. The Examiner urges that the combination of the antibody with chemotherapeutics has not been disclosed and that there are factors which would cause one of skill in the art to experiment;

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including the dosage of chemotherapeutics and antibody needed, the side effects associated with the combination of chemotherapeutics, the clearance rates of the antibody, and whether the combination of antibody and chemotherapeutics is even effective. The Examiner urges that no where does the specification teach an antibody that is capable of "cross-blocking" 4D5, 7C2 and 7F3 and relies on Seaver, S. for the proposition that the screening of antibodies, although possible, is not an easy task, of which "a minimum of 1000 clones need to be screened to find 1-2 monoclonal antibodies."

Applicants submit that the presently claimed invention is enabled by the disclosure.

First, Applicants will demonstrate that the presently claimed methods have *in vivo* therapeutic efficacy. Applicants rely on objective evidence in the form of published human clinical trial results demonstrating that *in vivo* therapy with an anti-ErbB2 antibody, namely humanized 4D5; Trastuzumab (HERCEPTIN®), and Vinorelbine (sold under the trademark NAVELBINE®) is effective.

Burstein *et al. J. Clin. Oncol.* 19(10): 2722-2730 (2001) is attached which details clinical activity of Trastuzumab and Vinorelbine in HER2-overexpressing cancer patients. Based on the study, Burstein concludes that the anti-ErbB2 antibody Trastuzumab in combination with Vinorelbine is highly active and well tolerated. Thus, Applicants submit that therapy with an anti-ErbB2 antibody and Vinorelbine as claimed in the present application is indeed effective *in vivo*. Further human clinical trial results confirming this to be the case include those reported in Filipovich *et al.* "Chemotherapy with trastuzumab plus vinorelbine in patients with erb-B2 overexpressed tumor is active in metastatic breast cancer" Abstract #436 presented at SABCS Meeting 2002 (copy attached); and Chan *et al.* "Multinational phase II study of navelbine (N) and herceptin (H) as first-line therapy for HER2-overexpressing metastatic breast cancer (HER2+ MBC)" Abstract #434 presented at SABCS Meeting 2002 (copy attached).

With respect to identifying antibodies that are capable of "cross-blocking" 4D5, 7C2 and 7F3, Applicants submit that the specification

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provides detailed guidance therefor at page 12, line 24 through to line 7 on page 13; and page 32, lines 27-30. Even though a large number of antibodies may need to be screened, this is considered routine experimentation in the antibody field as evidenced by Seaver.

Applicants submit that the presently claimed invention is enabled by the present disclosure. Reconsideration and withdrawal of the rejection is respectfully requested.

Section 102(e)

Claims 42, 44 and 59-64 are rejected under 35 USC Section 102(e) as being anticipated by Hudziak *et al.* (US Patent No. 5,720,954).

The rejection is rendered moot by the amendment of independent claims 42 and 63 to recite "Vinorelbine." Human clinical trial results achieved using the claimed methods are reported in Burstein *et al.*, attached hereto. Those studies demonstrate that treatment with an anti-ErbB2 antibody, *e.g.* Trastuzumab, and Vinorelbine, is highly active and well tolerated (first sentence of Discussion on page 2728). Burstein further explains at the top of column 2 on page 2729 that the response rates seen in patients treated according to the presently claimed methods are higher than expected with single-agent therapy, suggestive of clinical synergy.

Reconsideration and withdrawal of the Section 103 rejection is respectfully requested.

Respectfully submitted,
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VERSION WITH MARKINGS TO SHOW CHANGES MADE

Please amend the following claims:

42. (Twice Amended) A method of treating a tumor or cancer characterized by overexpression or activation of ErbB2 comprising administering an anti-ErbB2 antibody and [a chemotherapeutic agent or growth inhibitory agent] Vinorelbine to a patient in amounts [effective] to kill or inhibit growth of tumor cells in the patient, wherein the tumor or cancer is selected from the group consisting of a liver tumor, colorectal tumor, prostrate tumor, pancreatic tumor, vulval tumor, thyroid tumor, hepatic tumor, sarcoma, glioblastoma, head and neck tumor, leukemia and lymphoid malignancy.

55. (Amended) The method of claim 42 wherein the anti-ErbB2 antibody binds to an ErbB2 epitope bound by [cross-blocks binding of] antibody 4D5 (ATCC CRL 10463) [to ErbB2].

56. (Amended) The method of claim 42 wherein the anti-ErbB2 antibody binds to an ErbB2 epitope bound by [cross-blocks binding of] antibody 7C2 (ATCC HB-12215) or antibody 7F3 (ATCC HB-12216) [to ErbB2].

Please cancel claims 59-62 without prejudice or disclaimer.

63. (Amended) A method of treating a tumor or cancer characterized by overexpression or activation of ErbB2 comprising a first therapeutic regimen comprising administering an anti-ErbB2 antibody to a patient in an amount [effective] to kill or inhibit growth of tumor cells in the patient and a second therapeutic regimen comprising administering Vinorelbine [a growth inhibitory agent] in an amount [effective] to inhibit growth of tumor cells in the patient [, wherein the growth inhibitory agent is a vinca].

Please cancel claim 64 without prejudice or disclaimer.

65. (Amended) The method of claim 63 wherein the anti-ErbB2 antibody

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binds to an ErbB2 epitope bound by [cross-blocks binding of] antibody 4D5 (ATCC CRL 10463) [to ErbB2].

66. (Amended) The method of claim 63 wherein the anti-ErbB2 antibody binds to an ErbB2 epitope bound by [cross-blocks binding of] antibody 7C2 (ATCC HB-12215) or antibody 7F3 (ATCC HB-12216) [to ErbB2].

Please cancel claims 67-68 without prejudice or disclaimer.

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